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# False elevations in urinary metanephrines: under-recognised pitfall with 24-hour urinary volume collection

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## SUMMARY

One pitfall in 24-hour urine collection is the input of incorrect urinary volume by the reference laboratory. This may lead to an incorrect diagnosis of pheochromocytoma or paraganglioma. A 48-year-old African-American woman was seen in the clinic for an elevated 24-hour urine metanephrine screen during workup for secondary hypertension. Urine volume was found to be incorrectly inputted by the lab as 9750 mL rather than 975 mL. The urinary metanephrines were then recalculated and the 24-hour urinary metanephrines resulted within normal limits. This case highlights this unique and potentially under-recognised error in testing with 24-hour urine volume collection.

## BACKGROUND

Since 1956, when Armstrong *et al* reported the presence of catecholamine products in the urine, testing methodologies have gradually improved in detecting pheochromocytoma and paraganglioma (PPGL).<sup>1</sup> The measurement of fractionated 24-hour urinary metanephrines is now one of the standard first line tests to detect PPGL.<sup>2</sup> Detection accuracy and precision of urinary metanephrines have improved further with implementation of mass spectrometry.<sup>3</sup> Even with improved accuracy in analytical results, the 24-hour urine collection in the real world can be fraught with errors. Specifically, errors in urine results can occur in the pre-analytical phase, defined as the errors that occur from physician order to the point of laboratory testing.<sup>4</sup>

These errors in laboratory medicine can occur despite dedicated technicians with high-quality processes in place to avoid such errors. The frequency of laboratory errors is reported at a rate of 0.012%–0.6%.<sup>5</sup> Since 80%–90% of the clinical decision making is based on labs, this small percentage can substantially affect patient care.<sup>5</sup> Clinicians should be cognizant of this possibility and this case highlights the errors that can occur with 24-hour urine collection and approaches to avoid these diagnostic pitfalls.

## CASE PRESENTATION

A 48-year-old African-American woman was referred to the endocrine clinic for treatment of PPGL. Endocrine workup for thyroid disorder and hyperaldosteronism was ruled out, but she was found to have marked elevation in 24-hour urine metanephrines. She was diagnosed with PPGL and underwent further evaluation with CT scan of the

adrenals that did not identify any adrenal nodules or abnormalities.

She was referred to the endocrine clinic for further evaluation. Her workup was notable for two episodes of hypertensive urgency where she required treatment in the emergency room. She denied any symptoms of pheochromocytoma. She was on metoprolol, valsartan and chlorthalidone for blood pressure control. No other significant medical conditions reported. She denied any family history of PPGL, early heart disease or stroke. Physical examination was overall unremarkable. Her laboratory data reported marked elevation in urinary metanephrines at 995 µg/24 hours (normal 45–290 µg/24 hours) and normetanephrine at 3393 µg/24 hours (normal 80–500 µg/24 hours). However, both 24-hour urinary and plasma metanephrines were repeated and resulted within normal limits.

## OUTCOME AND FOLLOW-UP

Due to the significant discrepancy in results, her prior urinary samples were scrutinised. The reference laboratory was contacted, and it was discovered that the measurements were calculated with a urinary volume of 9750 mL. After querying the patient, she reported a urinary volume of approximately 1 L. It was deduced that the actual urinary volume was 975 mL and not 9750 mL. The urinary metanephrines was recalculated and the 24-hour urinary metanephrines resulted within normal limits at 99 µg/24 hours for metanephrines and 339 µg/24 hours for normetanephrines. The patient was reassured of results and blood pressure was optimised with adjustment in antihypertensive medications. No further medical issues were reported.

## DISCUSSION

The measurement of fractionated 24-hour urinary or plasma metanephrines (metanephrines and normetanephrines) is the standard first-line screen for PPGL. There is controversy on which is considered the best initial screening test.<sup>2</sup> Plasma metanephrines have a higher sensitivity (96%–100%) but it is less specific than 24-hour metanephrines (77%–89%).<sup>6</sup> Twenty-four-hour urine metanephrines have a sensitivity of 97% and a specificity of 85%–91.1%.<sup>6,7</sup> Measurement of 24-hour metanephrines combined with 24 hour urine catecholamines increases the specificity to 98%.<sup>7</sup> Sawka *et al* at Mayo Clinic has proposed measurement of the two methods based on pretest probability of PPGL.<sup>6</sup>



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In patients with high suspicion for PPGL, the recommendation is plasma metanephrines.<sup>6</sup> In patients with low pretest probability of PPGL, the recommendation is 24-hour urine metanephrines. Though this is the standard recommended practice, institutions often use plasma metanephrines as an initial screening test because 24-hour urine collection can be fraught with errors and burdensome to patients.<sup>2</sup>

Preanalytical errors in collection of 24-hour urine is quite frequent, with studies reporting a collection accuracy of 50%–51%  $p=0.017$ .<sup>8–10</sup> Undercollection or overcollection of 24-hour urine is the most common error in urinary collection accuracy.<sup>8</sup> Excessively high urine volumes will lead to false elevation, and low urine volume collection will conversely lead to falsely low results. Despite detailed instructions, one-third of the patients changed their fluid intake habits to increase urinary volume.<sup>11</sup> Another complicating factor is the possibility of using the wrong urine preservative for the 24 hours urine collection. Interestingly, in our patient's case, the error occurred with actual input of laboratory data. With urine collection, the volume must be manually entered by the laboratory technician to calculate the 24-hour urine laboratory result. The frequency of errors that occur from incorrect technician input is unknown, but this specific type of error is believed to be a unique cause of an abnormal 24-hour urine result. Given that the laboratory errors from a human factor is high as 80%, it is possible that this error may occur more frequently than recognised.<sup>12</sup> To avoid this possibility, the clinician should always review and confirm that the urine volume is appropriate for the 24-hour collection. By using basic stoichiometry, we were able to calculate the actual patient's urinary metanephrines based on the aliquot and corrected urinary volume.

Due to issues associated with 24-hour urine collection, guidelines for PPGL recommend measurement of 24-hour urinary excretion creatinine to verify completeness. Collecting creatinine simultaneously with metanephrines can help confirm adequacy. Daily creatinine excretion is approximated at 20–25 mg/kg of lean body weight in males and 15–20 mg/kg of lean body weight in females up to 50 years of age.<sup>13</sup> There is a gradual decline in creatinine beyond 50 years of age due to loss of muscle mass. Other formulas are available that take race, sex and serum phosphate into account in estimating creatinine.<sup>14</sup> Another study has validated use of a creatinine ratio formula to correct for overcollection and undercollection of 24-hour urine results.<sup>15</sup> Though measured 24-hour creatinine cannot be assumed to guarantee accurate measurement, it can help as a surrogate in assessing collection accuracy.<sup>14</sup>

A 24-hour urine collection will likely remain the standard for PPGL screening, but there have been alternative collection strategies proposed in detecting urinary metanephrines. Since catecholamines have a diurnal excretion, morning urine void was shown to be effective with similar diagnostic sensitivity and specificity as 24-hour urine collection.<sup>16 17</sup> Other studies have proposed the potential of spot urine metanephrine to creatinine ratios via direct electrochemical measurement.<sup>16 18 19</sup>

In summary, a 24-hour urine collection is an important screening test to diagnose PPGL. Clinicians must be able to identify potential errors in a 24-hour calculation that occurs with urine collection. Identifying these errors will reduce diagnostic uncertainty and inappropriate treatment. This not only applies to detection of PPGL in urinary metanephrine collection, but also applicable to all 24-hour urine collection samples for other medical conditions.

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## Learning points

- ▶ A 24-hour urinary metanephrines may be falsely abnormal due to incorrect input of urinary volume.
- ▶ The clinician should review and confirm the urinary volume in all patients that complete a 24-hour urine volume collection to ensure results are accurate.
- ▶ The clinician may reduce uncertainty of appropriate 24-hour urine collection by pairing the collection with 24-hour urinary creatinine.

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